NON-TECHNICAL ABSTRACT

PHASE I/II STUDY OF AUTOLOGOUS HUMAN GM-CSF GENE TRANSDUCED PROSTATE CANCER VACCINES IN PATIENTS WITH METASTATIC PROSTATE CARCINOMA

No systemic therapy improves survival for metastatic prostate cancer (PCA). Prostate cancer is now the second most common cause of death from cancer in the US with an American dying on average every 15 minutes from metastatic disease. Interest in immunotherapy using gene therapy for PCA has been stimulated by the findings that cytokine transduced tumor vaccines can induce antitumor immune responses. We have conducted extensive laboratory studies using a strategy for inducing anti-tumor immune responses to non-immunogenic tumors including PCA. By inserting immunostimulatory genes into rodent tumor cells, and injecting them under the skin, systemic antitumor immune responses have been reproducibly induced, resulting in eradication of small amounts of implanted tumor at distant sites. The Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) gene in these model studies conferred the most potent antitumor effects so far compared to other cytokines tested. Efficient introduction of this gene in the model cancer vaccine cells was accomplished with the retroviral vector MFG-S. This efficiency made feasible the generation of genetically engineered human prostate cancer vaccines from individual patients. Using the MFG-S vector, we are able to prepare prostate cancer cell vaccines from over 90% cases in clinical trial simulations. The genetically engineered prostate cancer vaccine cells then secrete GM-CSF in the range that confers antitumor efficacy.

Lethal irradiation of the genetically engineered PCA cells did not diminish therapeutic effects of vaccine cells genetically engineered to secrete the GM-CSF gene in our published preclinical studies. Irradiation of tumor vaccines affords a measure of safety for human studies without compromising potential therapeutic efficacy. The identical approach is currently under ongoing phase I study in NIH RAC approved protocol 9303-040 for renal cancer. To develop this new strategy for the treatment of prostate cancer, safety of tumor vaccines produced by this procedure must also be established in a phase I (toxicity) study.

The overall objective of the phase I portion of the study is to evaluate the safety and tolerability of PCA vaccine cell skin injections using a vaccine derived from a patient's PCA cells prepared with human GM-CSF gene transfer. To help ensure safety, all tumor cell vaccines will be irradiated prior to injection. It is unlikely that the injections will benefit patients enrolled in the phase I portion of the trial with advanced tumor burdens of metastatic disease. The rat prostate cancer genetically engineered tumor vaccines were effective at eliminating up to about 10,000 cancer cells at distant sites. The rodent tumors double every two days while human prostate cancers double every 80 to 100 days. If safety is established, a phase II portion of the study will test efficacy with a dose determined from the phase I study. The cohort to be treated in the phase II study is a subgroup of prostate cancer patients most likely to benefit: they have mimimal residual cancer following anatomic radical prostatectomy, but have an early time to measurable PCA relapse. The PCA specific blood test Prostate Specific Antigen can be used as a biostatistically validated intermediate endpoint to test antitumor effects in the phase II portion of the study. Prevention or delay in PCA recurrence measured as PSA recurrence free survival following adjuvant therapy with GM-CSF transduced, irraditated, autologous PCA vaccines is the efficacy endpoint of the phase II study.